ART. III.—SAPONIN, IN ITS RELATIONS TO PHYSIOLOGY.

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[Dr. Lautenbach's paper was written more than a year ago. Some more recent researches of his are added in the foot notes in brackets.—EDS.]

IN the present essay it is designed to treat in a brief manner of the physiological properties of a principle existing in a number of plants indigenous to America, which has, in the author's hands, yielded some interesting and important results. Important, in that it gives the physiologist a new agent to study certain of the functions of living tissues, which have hitherto been beyond his reach. Interesting, in that its action on certain tissues resembles that of no other known substance.

The glucoside saponin exists in almost all the caryophyllaciæ,* in all the agaves, as also in the *Polygala senega* and in the *Yucca baccata.*† It was first obtained by Schrade from the common soapwort (*Saponaria officinalis*). Shortly after Schrade, Bley‡ obtained it from the same plant. Later, Bussy§ found it in the oriental soapwort (*Gypsophila struthium*). It exists most abundantly, as was shown by Fleury and Boutier-Charland,‖ in the Brazilian soapbark.¶ Malapert determined its existence in the ovaries and fruit of the horse-chestnut.

*Among others in the *Gypsophila struthium*, *Lychnis diœceæ*, *L. chalcedonica*, *Saponaria officinalis*, *Agrostemma githago*, and *Siline inflata.*

†A recently discovered plant from southern Arizona, which is used by the inhabitants as a substitute for soap.

‡*Ann. Chem. et Pharm.*, IV., p. 283.

§*Ann. Chem. et Pharm.*, VII., p. 168.

‖*J. Pharm.*, IV., p. 249.

¶*Quillaya saponaria.* The bark of this evergreen tree has been used in the arts to remove grease-spots from cloth.

[The glucoside chamœlerin, discovered by Dr. Green (*Amer. Jour. of Pharmacy*, 1878), I have found to act physiologically in all respects like saponin, which it closely resembles.]

As usually obtained, saponin consists of a greyish-yellow powder of a sweetish taste, inodorous in the powdered condition, very soluble in water, but sparingly soluble in dilute alcohol, and entirely insoluble in absolute alcohol and ether. The watery solution froths like soap, and it is from this property that the substance gets its name. According to Rochleder and Schwarz its chemical composition is $C_{12}H_{20}O_7$. It is readily precipitated by soluble lead* and barium salts, and it to a slight extent reduces cupric oxide in the presence of an alkali.

Quevenne† determined this glucoside to be chemically identical with the polygalic acid from *Polygala senega*, and also that the physiological properties of the two substances were the same. The author's results on this point coincide with those obtained by this distinguished chemist.

GENERAL ACTION.

No cases of saponin-poisoning have as yet been reported, and we have to rely for our knowledge of the action of this substance on the human animal, on the reports of cases of poisoning from plants containing it. These are by no means rare in the European scientific and legal records of a third of a century ago. Numerous instances were then reported where agrostemma seeds were ground with the wheat in the preparation of flour, the ingestion of which produced poisonous symptoms. Two cases of poisoning in this manner were observed by Bonneau and Malapert,‡ and five cases came under the observation of Bellard.§

The symptoms observed were: general malaise, headache, vertigo, great difficulty in maintaining the upright posture, vomiting, increased secretion in the air passages, a hot skin, and a rapid, small pulse. In the more serious cases coma occurred, from which the poisoned person could only be

*On this account care must be taken in making a solution of saponin to use pure water, as water which has been standing in lead pipes frequently forms a precipitate.

†*Journ. de Pharm. et des Sciences Accessoires*, Sept., 1836, p. 449.

‡*Ann. d'hygiene Publ.*, XLVII., Avril, 1852, p. 350.

§*Casper's Vierteljahrschrift*, Bd. II., p. 100.

aroused by very powerful irritants. After death ulceration of the stomach and increased redness of this organ was observed.

If in other vertebrates saponin is introduced into the alimentary canal, the same symptoms are produced. In addition, however, there occurs an increased frequency of the respiratory movements, bloody fæcal discharges, and convulsions.* After death the stomach and intestines are almost always found reddened and softened, and at various portions of the alimentary canal extravasations of blood are found. The lungs are frequently in a hyperæmic state.

LOCAL ACTION.

On the skin.—One drop of a solution of saponin (1 gramme to 10 c. c.) applied to the unabraded skin, produces an unpleasant feeling, not amounting, however, to absolute pain. At the same time the skin, at the point of application, becomes more sensitive. This hyperæsthesia is sometimes accompanied by redness.

On the abraded skin the application is very painful, and is often followed by pustules. These latter are, however, limited to the portion of the skin to which the solution was applied. Redness is an invariable result of such an application.

On the mucous membranes.—On these the drug acts as a decided irritant. Inhaled into the nostrils it produces sneezing, and even painfully makes its presence known to the experimenter. At the same time a decided increase in the secretion of nasal mucus occurs.†

Applied to the *mucous membrane of the mouth* its original sweetish taste is soon followed by its irritant effects. These are manifested in an increased flow of the saliva, irritation of the fauces, accompanied by a scratching sensation which causes the person or animal to hawk for a long time after the application. The taste at the same time becomes burning or biting.

*The author has observed the ingestion of saponin to produce convulsions most frequently in birds, but they also occur in rabbits, cats, mice and dogs. In the dog the symptoms of poisoning above given occur only in exceptional instances, owing to this animal vomiting the drug.

†It is doubtless that powdered Quillaya bark owes its efficiency in cases of coryza to this property.

When by means of a stomach tube a solution of the drug is directly introduced into the *stomach*, these irritant properties become even more manifest. The animal retches continually; the respirations become more frequent, as does also the beat of the heart. In a short time vomiting results in dogs and cats; but even after this the symptoms of irritation continue for some time. If five grammes were thus introduced the animals frequently died from the gastro-intestinal irritation. After death the stomach and intestines were not only found reddened and softened, but were also the seat of numerous blood extravasations.

Inhaled into the *lungs* saponin produces marked irritant effects—coughing, hawking, etc.—accompanied by an increased mucus discharge from the air passages.*

On the skeleton muscles.†—Pelikan‡ found that, when he injected "1-2 gtt. of a syrupy solution of saponin" into the cellular tissue of a frog's leg, near the insertion of the gastrocnemius tendon, complete paralysis of the adjacent muscles was produced. Direct electrical irritation of the poisoned muscle, or of the sciatic nerve, failed to produce contractions in the muscles in whose vicinity saponin had been injected. The same observation holds good of curarized animals. The ligation of the abdominal aorta did not prevent this paralysis.

Pelikan's results were confirmed by Köhler.§

Przybyszewski‖ says that the muscular fibres at the point of injection are greatly changed, the striations in many places become invisible, and the single fibres lose their regular form.

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*From this it may be inferred that this drug will prove a valuable therapeutic agent in those cases where it is necessary to produce an increased bronchial discharge.

†Under the title "skeleton muscles" all the striated muscles except the heart are here included.

‡*Abh. d. St. Petersb. Acad.*, 3, 15 Oct., 1867. *Gaz. Méd. de Paris*, 1867, No. 45.

§"Die lokale Anæsthesirung d. Saponin." Halle, 1872, Pfeffer.

‖*Arch. of Exp. Path.*, V., pp. 137, 142.

[The anatomical changes produced in the striated muscles after the application of saponin are apparently identical with those produced by a temperature of 36° to 40° C., or by post mortem rigidity.]

In a large number of experiments made by the author on frogs, sparrows, pigeons, guinea-pigs, cats and dogs, an injection of a solution* of saponin always produced paralysis of the muscle into which the injection was made. The painting of the muscle with a similar solution produced the same effect. The strongest faradaic currents failed to cause the poisoned muscles to contract.

As the experiments made all lead to the same conclusion, several only will be here given as illustrations:

Experiment made May 23, 1877. *Rana pipiens.* Exposed gastrocnemius of right side. Galvanical irritation with the current from two small Daniell cells, causes decided movement in the muscle at 11.22 A. M.

11.22½. The muscle was painted with a solution of saponin.

11.24. The same irritation applied to the painted muscle no longer causes it to contract.

11.25. Irritation with a current from the Daniell cells fails to produce contractions.

Experiment made May 15, 1877. *Rana temporaria.* Irritation (galvanic) with two small Daniell cells.

9.17. Irritation of left gastrocnemius causes the muscle to contract 4-6 millimetres, as measured by means of Marey's myographion.

9.17½. The left gastrocnemius was painted with the solution of saponin.

9.19. Irritation fails to cause the painted muscle to contract, though the other muscles of the animal contract when directly irritated.

In the preceding experiments on frogs the muscles *seemingly* lost their irritability to galvanic currents on having a solution of saponin externally applied to them; numerous other experiments proved that the same result was obtained—as was already noted by previous investigators—when the drug is injected into the muscle, in the different varieties of frogs, as well as in pigeons and mammals.

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*1 gramme to 10 cubic centimetres.

[In the paper as written by Dr. Lautenbach several experiments are usually given in proof of each statement, but wherever they agree closely we will only quote one type-experiment.—EDS.]

The same results were obtained when the faradaic* irritation was substituted for the galvanic, and consequently it would be a needless sacrifice of space and time to give examples of experiments where this method of irritation was employed.

To what is this paralysis due? Being purely local it may be due to one of several causes.

1. The drug may so disintegrate the muscular fibres as to prevent them from executing their functions. If this were cause of the paralysis, the greater portion of the muscular fibres would be found disintegrated after the application of saponin to them. In numerous microscopic examinations of muscles painted with this drug, and whose contractility had thereby been abolished, I indeed found a small number of fibres disintegrated, but only those to which saponin was immediately applied were so affected. In the experiments where the solution was painted on the muscles, only the more external fibres were disintegrated, those lying deeper escaping, and yet the muscles were paralyzed.

This last mentioned fact suggests another explanation for the paralysis following the local application of saponin, namely:

2. That the disintegrated muscular fibres act as a barrier to the passage of the electric current to the still healthy portion of the muscle, and consequently the latter does not contract. That such a loss of the receptive power of the muscle may occur and yet the muscle be still able to contract from impulses conveyed by its nerve, was proven by the author in a large number of experiments. If this were the explanation for the want of irritability in the muscle after the application of saponin, the painted muscle must of necessity contract when its nerve is irritated. In all the experiments where, from the application or injection of the drug, the muscle failed to respond to irritants locally applied, irritation of the nerves also failed to cause the poisoned muscles to contract; thus proving that the cause of the paralysis affected the whole muscle, and not only those portions which were disintegrated.

*The apparatus used was a Leclanche cell with the Valentin modification of the DuBois-Reymond induction coil.

3. A drug may act as an irritant to the muscles, causing them to contract. Under these circumstances, the muscle being already contracted, a second irritation will have little or no effect, and the experimenter would be very likely to mistake the effects of a continued irritation for muscular paralysis.

Saponin is such a muscle-irritant. When applied to the gastrocnemius muscle, the latter very gradually contracts until its transverse is at least one-half the size of its longitudinal axis.

The following are illustrative experiments:

Time.	No. of Gal. Irritations.	Height of the Contractions.		REMARKS.
		From the Application of the Current.	From the Application of Saponin.	
Oct. 9, 1877.				*Rana esculenta.* After destruction of the brain and spinal cord the gastrocnemius of one extremity was removed and attached to Marey's myographion.
2.15	1	10.9 mm.		
2.17	2	9.5 "		
2.18			6.4 mm.	The muscle was painted with a solution of Saponin.
2.19	3	2.7 "		
2.20	4	1.8 "		
2.20.30			8.9 "	
2.21	5	0.6 "		
2.21.30			9.9 "	
2.22	6	0.4 "		
2.22.30			10.1 "	
2.24		0 "		
2.25			10.2 "	

In the above, as also in the following experiments, the painting of the muscle with saponin produced a gradually increasing contraction, independent of the action of any other irritant. The degree of this contraction when added to the

degree of the contraction still produced by the galvanic irritation, shows the contraction resulting from the combined action of these two dissimilar irritants simultaneously applied. It is also seen that the effects of galvanic irritation are gradually abolished.

Time.	No. of Gal. Irritations.	Height of the Contractions.		REMARKS.
		From the Application of the Current.	From the Application of Saponin.	
Oct. 10, 1877.				*Rana esculenta.* In this experiment the sciatic nerve was galvanically irritated instead of the muscle.
3.06	1	5.6 mm.		
.08	2	3.5 "		
.08.30			8.3 mm.	Painted gastrocnemius with saponin.
.10	3	0. "	9.5 "	
.11	4	0. "	11.6 "	
.13	5	0. "	12.9 "	
.20	6	0. "	14.6 "	

In other experiments the galvanic or direct current was substituted by the induction or interrupted current. The induction apparatus used was that of DuBois-Reymond as modified by Valentin. The current employed was derived from a single Leclanche cell. Pflüger's modification of the Helmholtz myographion substituted that of Marey. The result was the same as in the preceding experiments.

These experiments show conclusively that muscles previously painted with saponin cease to contract, simply because the application of this drug irritates, and causes them to contract to their utmost, when, of course, no new irritation will cause any further contraction. Consequently such muscles are no longer irritable.

Saponin being a muscle-irritant, it behooves us to determine the nature of the irritation. Is this irritation neuro—or idio—muscular? In other words, does the drug irritate the nerves in the muscles or the muscular fibres themselves? An irritation of the nerves of a muscle produces *immediate* contraction

of all the fibrillæ of that muscle. From the application of saponin the contraction is more gradual and occupies five, six, and even more minutes, in reaching its maximum. In this respect it approximates closely what Schiff has called the "*idio-muscular*" contractions." * If the contractions from saponin be of this variety, only the fibres directly involved by the drug will contract, while the remainder of the muscle will be quiescent. This contraction of the individual fibres will be manifested by their forming a protuberance over the level of the surrounding non-poisoned muscular fibres.

Such is indeed the effect seen when a pointed stick, previously dipped into a solution of saponin, is applied to a limited portion of a muscle, care being taken not to produce a mechanical irritation through the agency of the stick. Under these circumstances the part to which the drug has been applied is seen to gradually rise above the *niveau* of the surrounding fibres, and as gradually to return to its original position.

CONCLUSION.

Saponin directly applied to the skeleton muscles acts as an irritant, and produces an idio-muscular contraction. When this contraction has reached, or nearly reached, its maximum, the poisoned muscle ceases to respond to electrical irritations applied to the nerves or to the muscle itself.

Local action on the visceral muscles.—On the striated visceral muscles.—When saponin is directly applied to the heart of

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* *Lehrbuch d. Physiologie*, I., p. 21.

[When a weak solution of saponin is gradually injected into the heart of a frog, in whom the spinal cord and brain have been destroyed, it has a number of times been my fortune to find the skeleton muscles absolutely paralyzed as regards their neuro-muscular contractility. The muscles were by no means contracted by this injection; the idio-muscular contractility remained. When the injection was pushed further the idio-muscular contraction occurred, and the muscles shortened and became much harder to the touch. I have been able to produce the same effect locally in mammals by injecting the solution very gradually into the femoral artery. In saponin we therefore have a substance which, when carefully applied, can destroy the activity of the nerves in the muscles, without affecting the proper or idio-muscular contractility.]

a frog the movements of this muscular viscus gradually become slower and less extensive, until they cease entirely.

Oct. 12, 1877. Experiment on a frog, *R. temporaria.*

1.54. Exposed the heart. Heart-beats, 22 per minute.

2.03. Painted the heart with saponin.

2.06. Heart movements less marked.

2.10. 18 heart-beats per minute.

2.15. 15 " " " "

2.20. 4 " " " "

2.23. The heart's movements have ceased, and the muscle itself is no longer irritable. Reflex movements continue until 2.40.

July 2, 1877. Experiment on a frog, *R. pipiens.* Exposed the heart.

9.47. 31 heart-beats per minute.

9.49. Painted heart with saponin.

9.52. 24 heart-beats per minute.

9.55. 19 " " " "

10.01. 12 " " " "

10.04. 8 " " " "

10.10. 3 " " " "

10.12. The movements of the heart have ceased. The muscle itself is no longer irritable. Reflex movements continue.

The results obtained in the foregoing, and in a large number of similar experiments, might possibly be due to either a direct, or a reflex effect on the nerve centres. But as the same result was obtained in many experiments when both the brain and spinal cord have been previously destroyed, and even from the heart removed from the body, it must be concluded that this diminution of the heart's pulse, in frogs, is due to a direct action on its muscular fibres. When the central nervous system is destroyed, and saponin is injected into the *interior* of the heart, the same result is obtained.

In a manner similar to the above I have made numerous experiments on cats and rabbits. In rabbits the injection of .015 gram. and in cats the injection of .025 to .05 gram. of saponin into the heart, produced immediate cessation of the functions of that organ. That the electric cur-

rent present in all muscles still persisted in these functionless hearts, was proved by the method which I first made use of in 1874 while engaged in determining the physiological properties of conium. This method consists in opening the pericardium, and then bringing the phrenic nerve in contact with the heart-muscle, when it will be observed that the diaphragm contracts. On taking the nerve from the heart, again frequently a second contraction occurs. When the hearts of mammals are paralyzed by the direct action of saponin, this phenomenon can still be produced.

These results justify the conclusion, that, *saponin locally applied to the heart, directly paralyzes this muscle.*

On the other striated visceral muscles, the *diaphragm*, saponin, locally applied, also acts paralytically, as injections into it always produce great interference with the inspiratory movements of mammals.

Action on the non-striated visceral muscles.—For obvious reasons my observations on this subject have not been very extensive. They have indeed been limited to the muscular coat of the intestines, and any one who has investigated the local action of drugs on these structures need not be told with what great uncertainty such experiments are conducted. The almost absolute impossibility of determining whether an apparent increased movement of the intestines *is* only apparent, is among the least of the drawbacks, for even if an increased peristalsis occurs after a drug has been painted or injected into the intestinal walls of an animal, it is still questionable whether this increased peristalsis was not due to causes other than those produced by the drug.

In my experiments: 1, the peristaltic action of portions of the intestines into the walls of which a saponin solution had been injected, or on which the solution had been painted, still occurred; 2, there was a very apparent increase in the peristaltic movements produced a short time after the application

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[When a weak solution of saponin is injected slowly into the heart of a frog, or rabbit, the heart very frequently ceases to beat in diastole. Should the injection be continued, an "arrest in systole," as Köhler calls it, *i. e.*, an idio-muscular contraction of the entire heart-muscle is produced.]

of the drug. This increased peristalsis may have been due to other causes than the drug.

Local action on the nerves.—The efferent nerves.—Pelikan and other observers have long since noticed that a solution of saponin applied directly to the nerves destroys the excitability of these tissues. My experiments have shown that this conclusion is true as far as it goes, but it does not go far enough. The increased excitability of the nerves which precedes the loss of function produced by saponin, has been observed by no previous experimenter, although on this subject numerous investigations have been made. The previous investigators failed to see this increased excitability because they made all their observations with the eye. Had the myographion been used this action would certainly have been observed.

In the earlier experiments I committed the same error as did Pelikan and Köhler, in not *measuring* the degree of excitability of the nerves, and consequently the conclusion was arrived at, that the sole action which the glucoside exerts on the efferent nerves is to diminish their excitability. Later, in the experiments made with the aid of the Marey and Pflüger myographions, different results were obtained.

The method resorted to in these latter experiments was to remove the gastrocnemius and sciatic nerve of a frog, and attach the former to the lever of the myographion. The nerve was placed on a cork and moistened with a 0.7 per cent. solution of chloride of sodium. The electrodes from a faradaic or a galvanic battery were applied to the nerve, each electrode being ten millimetres from its companion. A Valentin hammer was used to make and break the current.

[In some recent experiments the lower portion of the intestine of a frog recently killed was connected with a Ludwig's manometer. The intestine was filled with a solution of bicarbonate of sodium and tied at the stomach. A solution of saponin was now applied to the intestine, whereupon the mercury began to rise slowly in the manometer until the pressure had mounted to nearly thirty millimetres of mercury. Since this was a constant result, it can be concluded, that saponin irritates the unstriped muscles of the intestines as it does the striated heart and skeleton muscles.]

Time.	No. of Irritations.	Irritation.	Height of Contractions.	REMARKS.
Oct. 10, 1877.		Galvanic. 2 Small Daniell's.		*R. esculenta.*
1.45	1		2.2 mm.	
1.46	2		2.1 "	
1.47				Painted the portion of the nerve between the electrodes with saponin.
1.49	3		5.5 "	
1.52	4		1.7 "	
1.55	5		0. "	
Oct. 10, 1877.		Galvanic. 2 Small Daniell's.		*Rana temporaria.*
2.04	1		1.1 mm.	
2.05				Painted as in last experiment.
2.07	2		1.6 "	
2.10	3		0.3 "	
Oct. 9, 1877.		Induction Current. 2 in. covered.		*Rana temporaria.*
1.55	1		34.8 mm.	
1.56	2		34.9 "	
1.57½				Painted nerve as before.
1.58½	3		51.8 "	
2.00	4		64.4 "	
2.02½	5		64. "	
2.05½	6		55.8 "	
2.14	7		40.4 "	
2.18	8		32.3 "	
2.23	9		28.5 "	
2.31	10		9.7 "	By 2.30 the muscle ceased to contract when the nerve was irritated.

From the foregoing experiments it will be seen that the local application of a solution of saponin to an afferent nerve,

produces an increased, followed by a diminished excitability, and, finally, by a total abolition of the functions of the portion of the nerve poisoned. The application of a solution of the drug to a nerve frequently produces contractions in the tributary muscles, showing that the drug acts on them as an irritant.

The primary increased excitability must be due to one of two causes: Either the nerve, when painted with the drug, becomes a better conductor for impressions received, or it offers less resistance to the reception of an irritation. If the former were the cause, irritation of a portion of the nerve situated to the central side of the part poisoned, would also produce an increased contraction of the muscle, after the lower portion of the nerve had been painted with saponin. This I have found not to be the case. The painting of the nerve with saponin did not, in the beginning, in the least influence the height of the contractions produced by irritation of the nerve above the part painted. The cause must, therefore, be sought in a decreased resistance offered to the reception of an irritation at the point to which the drug has been directly applied.*

The diminished excitability, which follows the primary augmented excitability, is due to a detrimental action on the conducting elements of the nerves themselves, as it is manifested not only at the point of application, but also in all portions centrally situated from this point.

CONCLUSION.

Saponin directly applied to an efferent nerve, first excites and then paralyzes it. The excitation is due to an increased receptive power (i. e., a decreased resistance to the reception of the irritation) at the point of application. The secondary paralysis is due to an interference with the functions of the conducting elements of the nerve.

On the afferent nerves.—Experiments on *frogs.* When a solution of the drug is directly applied to the sciatic nerve of

*The difference between the receiving and conducting properties of nerves was first alluded to by Schiff (*Lehrb. d. Phys.*, I., 1859), and has since been proven by the author.

a frog, it first of all increases the reflex excitability of the part on which it is painted. This increased excitability was proven by applying to a "saponized" nerve an electric irritation, which was previously not strong enough to produce reflex contractions in the opposite limb; while after the application of the drug, the same current was found to produce marked reflex contractions. As with the efferent nerves, this increased excitability is soon followed by the reverse effect; and in a very short time strong electrical irritations fail to produce any reflex contractions whatsoever. The sensory nerves of frogs are, therefore, first excited and then paralyzed by saponin.

On the afferent nerves of *mammals* the results obtained will prove of great interest to physiologists, who in saponin will find an important agent to determine the presence of afferent nerves in organs where their presence has long seemed doubtful. When a solution of the glucoside is injected into an efferent blood-vessel, a rise in the blood pressure is observed. As will be shown later, this rise is caused by a stimulation of the vaso-motor "centres." When, however, the afferent nerves of a limb or organ into which the drug is injected have previously been cut, this increased blood pressure fails to occur, and, consequently, must be due to a direct irritant action of the drug on these afferent nerves, causing a reflex stimulation of the vaso-motor "centres."

Saponin is the only substance at present known to have such an action.

To determine whether an organ possesses afferent nerves or not, it is only necessary to inject a solution of the glucoside into the artery of the organ in doubt; and if the arterial pressure immediately rises, that alone will be presumptive evidence of the presence of sensory nerves. If, however, the nervous communications with this organ are now cut, and it is found that a rise in the pressure no longer follows the injection of the drug, it is proven, beyond a doubt, that the organ contains afferent nerve fibres.

I have proven in this manner the presence of nerve fibres in the brain, which are afferent to the vaso-motor "centres" in the medulla oblongata. An injection of saponin into the carotid artery (internal), produces an immediate rise in the

arterial pressure. This might be due to a direct action on the vaso-motor "centres" themselves; but as it failed to occur after section of the pons, though the poison still reached these "centres," the conclusion was inevitable that by this section I destroyed fibres which carried the impression made by saponin to these "centres." These experiments led to another very interesting observation, namely, the course which the vaso-motor fibres take after they leave the medulla oblongata. In two experiments, one on a rabbit and the other on a dog, I cut the whole of the posterior four-fifths of the cervical spinal cord, immediately below the calamus. An injection of saponin was then made into the internal carotid artery, when an immediate increase in the arterial pressure occurred, showing conclusively that the vaso-motor fibres of the spinal cord had not been cut. An injection into the femoral artery in these animals had no immediate effect on the blood pressure; and, consequently, the sensory fibres of the cord must have been cut. The vaso-motor fibres must at this point pass through the anterior fifth of the cord.

The method employed appears so certain, that physiologists will, no doubt, adopt it to further determine the course of these nerves.

The only other organ which I have thus far searched for afferent nerves, is the liver. The efferent vessel used in these experiments, was the vena porta. An injection of saponin into this vein, produced an immediate augmentation in the arterial pressure. Concluding from this, that afferent nerves existed in this organ, the question, Which are the afferent nerves? presented itself. It seemed to me most plausible that these nerves were branches of the pneumogastrics; and I was, therefore, much surprised to find that, after section of both pneumogastrics in the neck, an injection of saponin into the liver still augmented the blood pressure.

It was, therefore, necessary to examine the other nerves which form the hepatic plexus for the afferent nerves of the liver. The only ones given by anatomists are branches from the two upper splanchnics, and from the phrenic nerves. Section of the latter I found not to influence the effect of the injection. The splanchnics could only be studied by ex-

clusion, as they are too intimately connected with the larger number of the blood-vessels of the body, to admit of their section without vitiating the results. The splanchnics receiving filaments from the spinal cord as low down as the eleventh dorsal vertebra, a section of the cord was made one vertebra below this. On injecting saponin into the liver of an animal thus prepared, no increased arterial pressure was observed. As an injection of the glucoside into one of the thoracic arteries still affected the blood pressure, it must be concluded that the afferent nerves of the liver are not branches of the pneumogastric, splanchnic, or phrenic nerves; but are hitherto undescribed nerves, entering the spinal cord below the twelfth dorsal vertebra.

There are other evidences of an excited neurility of the afferent nerves following the introduction of the drug into an efferent (from the heart) blood-vessel. Thus, for instance, an injection of .15 gram. of this substance into the femoral artery of a cat or rabbit, produces convulsions, which, for reasons to be given shortly, I ascribe to the direct stimulation of sensory nerves.

Convulsions may be produced by a drug in four different ways: First—they may be cerebral; second—they may be spinal; third—they may be due to stimulation of the peripheral ends of the motor nerves; fourth—they may be caused reflexly by stimulation of the peripheral ends of the sensory nerves.

That the convulsions are not due to a direct stimulation of the peripheral motor nerves was readily proved by tying the iliac artery of one side in various animals and then injecting saponin peripherally into the femoral artery of the opposite side, when convulsions uniformly occurred over the whole body. Were they due to a direct action on the peripheral efferent nerves they would not have occurred in the limb where the access of the poison to the nerves was cut off.

Dec. 18, 1877. Experiment on a cat. Tied the right external iliac artery; placed the needle of the hypodermic syringe into the left femoral artery. 2:40 P. M.—Injected .15 gram. saponin into the left femoral artery, towards the periphery. 2:40:30 P. M.—Clonic convulsions, involving the

whole of the muscles of the extremities, including those of the right posterior extremity. These were followed by opisthotonos and tetanus, involving all four extremities. The animal recovered.

Dec. 27, 1877. On a rabbit. Tied right external iliac artery. Placed hypodermic needle in a branch of the left femoral artery — the needle pointing towards the periphery. 11:17 A. M.—Injected .1 gram. of the drug into this prepared artery. Immediate clonic convulsions were produced all over the body. The animal recovered.

Eight of these experiments were made, all giving similar results.

I was forced to conclude that these convulsions were due, not to a direct effect on the brain or spinal cord, but to stimulation of the peripheral sensory nerves, reflexly exciting the spasm-producing mechanisms in the spinal-cord or brain, for the following reasons:

1. Convulsions do not occur when the drug is injected into a vein of the general circulation. Were they due to a direct effect on the nerve centres they would occur even more readily if the drug was introduced into a vein, when it could the more easily reach the centres. It is true that convulsions frequently follow the subcutaneous introduction of the drug in mice; but as these occurred immediately after the injection, and it taking hours for the drug to be absorbed under these circumstances, these experiments only go to prove the correctness of my statement. These convulsions could only have been due to a direct action on the afferent nerves.

2. Convulsions were produced in cats and rabbits, in whom I tied the abdominal aorta and inferior *vena cava*, and then injected the drug into the femoral artery of one of the posterior extremities.

3. In a cat whose heart was paralyzed by chloroform, and in whom the circulation had ceased, an injection of .15 gram. into the left femoral artery, after previously tying the corresponding femoral vein, produced tetanic convulsions in all four extremities. In spite of the cessation of the circulation, this animal evidently had enough of the central nervous system intact, to translate the impression received from the afferent

nerves of the injected limb into tetanus-producing efferent impulses.

4. When the nervous communications between the centres and the limb, into whose efferent vessels saponin is injected, are destroyed, convulsions will not only fail to occur in that limb, but will also fail to be present in any other portion of the body. Thus, for example, in animals where I cut the anterior crural and sciatic nerves of an extremity, and then injected a solution of the drug into an artery of the same extremity, no convulsions were produced, nor were any symptoms manifest for hours. If, on the other hand, the nerves were allowed to remain intact, convulsions occurred immediately on the injection of the drug. In the same manner, an injection into the vena porta will produce *immediate* convulsions, extending over the whole of the body; and as these no longer occur anywhere when the spinal cord is cut at the twelfth dorsal vertebra, it must be conceded that they are due to a direct action on the afferent nerves of the liver.

That the brain contains nerve fibres which are afferent to the vaso-motor "centres" was demonstrated on one of the previous pages. Either these fibres or others contained in the brain are afferent to the spasm-producing mechanisms of the central nervous system. This was shown in my experiments, by the occurrence of convulsions immediately on introducing the drug into the internal carotid artery, and their non-production by such an injection after section of the pons immediately below the corpora quadrigemini, when, evidently, the connection of the fibres, stimulated by the drug with the so-called spasm-centre, or centres, was destroyed. After this operation, however, convulsions still result from an injection into the femoral artery.

Having shown that this symptom of saponin-poisoning is due to a direct stimulation of the peripheral afferent nerves, it remains still to be determined whether the stimulation

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[When the entire central nervous system of a frog is destroyed, and a very strong solution of saponin is injected through the heart into the abdominal aorta, tetanus of the posterior extremities occurs. This is probably due to a direct action on the nerves. This tetanus is in a short time replaced by the idio-muscular contraction of the muscles.]

reflexly excites the spasm-"centres" of the brain or those of the spinal cord.

For the following reasons it was concluded that the former and not the latter are reflexly excited:

1. When, through the introduction of saponin into the femoral artery, convulsions were produced, these immediately ceased on making a section of the medulla oblongata at the calamus; nor could they be again brought on by fresh injections of the drug. Were they due to a reflex excitation of the spinal spasm-"centres" they must have continued even after the section; but as they ceased immediately on breaking the connection of the brain with the nerves affected by the drug, the inevitable conclusion is that the structures reflexly affected in producing these convulsions must be in the brain.

2. When an injection of the drug is made into the femoral artery after section of the medulla oblongata at the calamus, no convulsions occur.

The conclusions to be drawn from the above given facts are, that *the saponin convulsions are due to a direct stimulation of the peripheral afferent nerves, reflexly exciting the convulsion-producing mechanisms in the brain.*

Thus far the convulsion-producing mechanism has been limited, by the experiments above referred to, to the portion of the central nervous system limited by the corpora-quadrigemina above and the calamus below. To determine whether or not this "centre" is located in the medulla oblongata, I, in a number of experiments on cats, cut this organ at its junction with the pons. On now introducing the drug into an efferent blood-vessel of one of the extremities, no convulsions were produced, showing that the spasm-"centres" reflexly affected by saponin are situated somewhere in the pons, and not in the medulla oblongata. This corresponds to the observations of Nothnagel,* who also locates these "centres" in the pons.

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* *Virchow's Archiv*, B. 44, H. 1, p. 1.

[Since the above was written, Luschsinger has shown, that certain precautions are required to demonstrate the action of convulsive agents on the spasm-centres situated in the spinal cord (*Pflüger's Archiv*).]

CONCLUSIONS.

Directly applied to the afferent nerves of frogs, saponin first acts as an exciting, and then as a paralytic agent.

The afferent nerves of mammals are excited by the direct action of the glucoside, producing reflexly an augmented blood pressure and convulsions.

The increased blood pressure is due to the excitation of the afferent nerves, reflexly producing a stimulation of the vaso-motor mechanism in the medulla oblongata.

The convulsions are due to the same excitation reflexly stimulating a spasm-producing mechanism in the pons.

Action on the spinal cord.—Köhler* found that when the brain of a frog is destroyed, and a saponin solution is directly applied to the spinal cord, convulsions result. In the author's experiments the same effect was observed, but it was soon followed by spinal paralysis and complete abolition of reflex activity. Convulsions were never observed from this local action on the cord, so long as the brain remained intact.

The following are illustrative experiments:

Dec. 19, 1877. Experiment on a frog, *R. esculenta.* Exposed the spinal cord below the origin of the nerves of the anterior extremities. Painted the exposed portion of the cord with a solution of saponin. In two minutes, irritation of a posterior extremity causes reflex movements in it and its fellow, but not in the anterior extremities. Irritation of an anterior extremity causes reflex movements in the anterior portion of the animal, but not in the posterior portion. This shows that the conducting power of the spinal cord has been lost between the origin of the anterior and posterior nerves. In five minutes convulsive twitchings were manifest in the toes of the posterior extremities. At the end of seven minutes these twitchings ceased, and reflex movements could no longer

*"Die lokale Anæsthesirung d. Saponin," Halle, 1872.

[But if saponin is directly injected into the medulla oblongata, a tetanus lasting a few minutes only, is immediately produced, after which it is absolutely impossible to bring about any reflexes in the frog, although the motor nerves are still excitable.]

be excited, though they still occurred in the anterior extremities.

July 30, 1877. Experiment on a frog, *R. esculenta.* The spinal cord was painted with saponin, the brain being left undisturbed. In five minutes complete paralysis, both reflex and voluntary, of the posterior extremities. No convulsions. In ten minutes the convulsions had not appeared.

Action on the brain.—The brain of the *frog* being so subordinate a portion of the nervous system, as compared to the spinal cord in this animal, I was not surprised to find the application of saponin to their brains produce no *apparent* symptoms. This absence of symptoms was, however, only apparent, as on closer examination it was found that the tactile sense* was lost, and that the tri-facial reflexes no longer occurred. The frogs whose brains had been thus treated, lost their sense of sight, and perhaps this will account for the backward movements of such animals. Reflex movements continued to occur. Convulsions were never observed. The animals usually recovered in five or six hours.

On pigeons similar effects were observed. After painting their hemispheres with a solution of the glucoside, these animals fell into a sleep, from which they wakened after some hours. From this state the animals could be aroused by strong irritants, but when the irritant was removed the symptom returned. The same backward movements were observed as in frogs.

On mammals.—In these animals various portions of the hemispherical convolutions were painted with saponin, when, for the time being, the functions of these portions of the cerebral lobes seemed to be entirely abrogated. For example, when the convolutions in the neighborhood of the sulcus cruciatus were painted, the peculiar paralysis of tactile sensibility was observed. These symptoms afterwards disappeared. From this it appears that a solution of *saponin directly applied to the cerebrum temporarily destroys the functions of the part involved.*

The injection of a few drops of the solution into the corpus

*Frogs always lose their tactile sense when the cerebrum is removed.

lenticularis* yielded interesting results. It has long been an object among physiologists to determine the cause of hemiplegia from cerebral lesions. Saponin is evidently a substance which will greatly assist in the accomplishment of this object. The explanation of this hemiplegia most universally adopted at present, is, that it is due to the destruction of certain portions of the brain, whose function is to preside over the movements of the opposite side of the body. This explanation would be quite plausible were it not that these portions of the brain have frequently been found entirely disintegrated in persons who never were hemiplegic. In dogs I have several times made a complete section of the brain on a level with the upper boundary of the corpora quadrigemina, without motor paralysis resulting. In a number of other experiments the whole of the corpus striatum and optic thalamus of one side were destroyed without ever producing hemiplegia. Cerebral hemiplegia not being due to the destruction of any of the great ganglia of the brain, it is somewhat difficult to determine why a hemorrhage into these structures so frequently produces hemiplegia. Apoplexy may possibly produce this symptom in three different ways: first, it may destroy the voluntary motion-producing nervous mechanism; second, it may through pressure influence this mechanism; third, it may irritate fibres concerned in motion, and thereby produce paralysis.

An injection of saponin into the corpus lenticularis produced hemiplegia of the opposite side of the body. That this effect was not due to pressure, or to the destruction of the part, was proved by experiments where water was injected into this portion of the nervous system without producing any paralysis. This hemiplegia from saponin is but temporary, it vanishing after some hours, and it was only observed in three experiments; but as this is the first instance on record† in which hemiplegia was traumatically produced in animals, it is well worth dwelling on.

Saponin must produce this effect through its irritative prop-

*The posterior portion of the corpus striatum.

†I have on other occasions, and by other agents, succeeded in producing hemiplegia in dogs and cats, and will in a later paper draw attention to these experiments.

erties, and as we have before seen that it is a local irritant to the peripheral nerve fibres, it is by no means improbable that it similarly affects the fibres in the brain. What at first sight appears improbable, is that an irritant applied to a portion of the nervous system can produce motor paralysis, an excitation of motor fibres being usually associated with motion. A number of other facts go to confirm the apparently improbable statement, that an irritant applied to nerve fibres may prevent these from exercising their functions. A well known fact, to which the writer has, within a short time, again drawn attention, is that a polarized* nerve, under certain conditions, fails to respond to irritants applied to it *anywhere*† throughout its course. Undoubtedly the pressure of saponin in the corpus lenticularis acts on fibres concerned in producing motion, as does the constant current on the ordinary nerves; and the consequent absence of movement in certain muscles is due to the polarization preventing the transmission of the voluntary motion-producing impressions.

Local action on blood, lymph, mucus and pus corpuscles.—The only previous investigation of the action of saponin on the blood-corpuscles was made by Przybyszewski,‡ and his experiments do not seem to have yielded any very positive results. This author found, that if a drop of a four per cent. solution of the drug was mixed with a drop of frog's blood, the stroma of the red corpuscles becomes pale, until only a granular nucleus remains visible—this latter only differing from the white corpuscles in being smaller and more oval. In his experiments on human blood, with a ten per cent. solution, he found (p. 140,) "in 3–5 minutes the upper surface of the cells to seem folded and contracted, and soon the red corpuscle becomes so pale that its stroma resembles a granular residue. In a few minutes the whole preparation was filled with irregularly-shaped pale corpuscles."

*A polarized nerve is one through which a constant or polarizing current is passing.

†Pflüger has denied this, but I have repeatedly demonstrated it to the satisfaction of several eminent physiologists, who were at first indisposed to believe it.

‡*Arch. f. exp. Path.*, V., pp. 137–142.

No doubt the preparation of the glucoside used by this experimenter was not all that could be wished, or he would have made the interesting discoveries in regard to this action of the substance which have fallen to the lot of the author. It may however be alleged, that the author's preparation of saponin was impure, and that the phenomena hereafter to be described were due to the specific action of the impurities. This objection might be plausible: first, if we knew of any other neutral substance which had a similar action on the blood; second, if the experiments had been made with but one specimen of the drug. Saponin from the Brazilian soapbark, from the American and Oriental soapworts, and from senega snake-root, all gave identical results. The water which was allowed to percolate through powdered soapwort, soapbark, or senega snake-root, was found to have the same action on the blood as saponin.

In studying this action, the lower classes of vertebrates will be taken first.

Action on the blood of *frogs.*—When a drop of saponin solution (1 gram. to 10 c. c.) is allowed to mingle with a drop of frog's blood, as with a flash the color of the red corpuscles becomes very faint, but every portion of these corpuscles remains visible. It appears as if the coloring matter of the corpuscles is dissolved, leaving behind only the frame-work. The granular nucleus of these corpuscles remains unaffected, and, on superficial examination, appears to be a lymph corpuscle, which it strongly resembles. Sometimes the frame-work of globulin also undergoes changes, and crystallizes, the crystals being elongated rhombs, and *colorless.** Much slower than the red, the white corpuscles are affected, and seem absolutely to disappear.

The cause of the red corpuscles becoming almost invisible,

*These crystals are in shape identical with the so-called hæmoglobin crystals, differing from these only in not containing any coloring matter. This, taken in connection with the fact that saponin can dissolve out the coloring matter of the hæmoglobin and allow the transparent colorless crystal to remain, makes it certain that the formation of blood-crystals may be entirely independent of the coloring matter, and that the latter, when present in them, must be looked upon as a chance production, as iron is in a quartz crystal.

is the dissolving out of the coloring matter, making the refracting angle of these corpuscles nearly identical with the refracting angle of the liquor sanguinis. That such was the case, I proved by adding a trace of tr. iodinii to frog's blood, previously treated with saponin, when almost instantaneously the red corpuscles again became very apparent; that is, the almost absolute invisibility of the red corpuscles is overcome by placing around it a fluid of a different refracting power.* The invisibility of the white corpuscles continued, in spite of the iodine, making it very probable that these were dissolved. The lymph corpuscles were not affected by either the saponin or the iodine solution.

On the blood of *pigeons.*—On applying a drop of the solution of the drug to the blood of these animals, and then examining the latter under the microscope, it was found that the red corpuscles—nucleus and all—had completely disappeared. In a few minutes the white corpuscles were also found to have disappeared. This vanishing of all the corpuscles must have been due to their being dissolved, as iodine failed to make them again appear.

On mammals.—First the red and then the white corpuscles disappear, on adding saponin to blood taken from mice, guinea-pigs, cats, dogs and men. On taking a drop of human blood, and placing it on a glass slide, and over it a cover-glass, and then placing at the edge of the latter a drop of the solution of the drug, the red corpuscles were seen to disappear immediately, while the white usually occupied at least five or six minutes before they too were dissolved. I say dissolved, because after such an experiment the tincture of iodine method failed to demonstrate the presence of morphological bodies. At a later period, frequently the microscopic slide was found to be covered with numerous transparent, colorless "hæmoglobin" crystals.

If a large quantity of blood, taken from a mammal, is mixed with a small quantity of saponin solution, and then allowed to stand, the blood will not coagulate for five or eight days. This

* The microscope employed was a Seyss; objective number, 5; ocular number, 1.

These experiments were made in the months of January and December.

great retardation in the coagulation of the blood treated with this drug, I find at present impossible to explain; but it is an interesting fact, and well worth recording. Blood treated in this manner, shows most beautifully the spectrum for oxy-hæmoglobin.

The "saponized" corpuscles do not reappear on adding iodine or carmine * to the preparation, and, consequently, their disappearance is not due to their refraction being made identical, or nearly so, with that of the blood plasma, through the hæmatin being dissolved away from the globin. Their disappearance is not due to the imbibition of water, as a drop of water placed on a slide, on which corpuscles have been prepared, is insufficient to make them indistinct.† It can also not be due to an inorganic chemical solvent in saponin, this substance containing only oxygen, hydrogen and carbon, and being of a neutral reaction. The most careful chemical examination failed to detect traces of any of the alkalies. From these facts it must be concluded that the glucoside is a solvent for the red as well as the white corpuscles of mammals.

Having come to this conclusion, it was necessary to determine what percentage of the glucoside was necessary in order for the solution to have its peculiar effect on the corpuscles. It was found that sometimes, but not always, a drop of a solution of saponin, of the strength of one part to two thousand parts of distilled water, would cause the solution of the corpuscles in three times its bulk of blood. A solution of the strength of one part to one thousand of distilled water constantly produced this effect.

When a microscopic slide on which is placed non-saponized blood, is slightly heated, *debris* of corpuscles immediately appear. If, however, "saponized" blood is so treated, the *debris* does not appear until the preparation is almost dry. Sometimes, on adding the drug to blood, *debris* of corpuscles appear, which may or may not, according to the prejudices of the observer, be considered as parts of corpuscular walls.

* Gaucher (*Arch. de Phys.*, IV., p. 770) found that when he dissolved away the coloring matter of red corpuscles, these could readily be stained with carmine.

† Water, in large excess, causes them to disappear.

When a large amount of the drug is introduced into an efferent* blood-vessel, such as the femoral artery or mesenteric vein, the corpuscular elements of the blood gradually become less numerous. This is more especially true of the red corpuscles, and we have, consequently, produced a pseudo-leucocythæmia, i. e., the colorless corpuscles are not more numerous than before, but through the solution of some of the colored corpuscles, they are, relative to these latter, increased in numbers.

Saponin being a solvent for colorless corpuscles, is it also a solvent for mucus and pus corpuscles? Without having made the necessary experiments, the inclination would be to answer this question in the affirmative, as the histologists teach us that these latter are colorless corpuscles which have migrated through the walls of the blood-vessels. Many histologists go so far as to say they are identical with the colorless corpuscles. No proof has, as yet, been furnished of the migrated colorless corpuscles being the pus and mucus corpuscles; though Waller, Cohnheim and others, have shown that the former do migrate; but that they become the latter remains still to be proven. The statement that these corpuscles are one and the same, rests solely on assumption, as they are not even morphologically identical in all respects.

Should the mucus, pus and colorless corpuscles of the blood be identical, it would be expected that they would all three be soluble in a saponin solution. When mucus is taken from the nose, mouth or œsophagus of man and other mammals, and treated with this solution, no effect is observed. After continuing the observations for several days, the mucus corpuscles were always found to remain unaltered. Pus taken from abscesses was treated in the same way, without any of the pus corpuscles being dissolved. It must, therefore, be concluded that pus and mucus corpuscles are not identical with the colorless corpuscles of the blood.

Another question which here suggests itself, is, whether or not these latter are identical with the lymph corpuscles from which they are said to originate. Lymph corpuscles obtained

* The drug could not be introduced in large quantities into a vein of the general circulation, for fear of producing the direct cardiac action.

from the thoracic duct and the lymphatic glands of mammals, or from the lymph sacs of frogs, are not in the least affected by saponin. So that the last query must also be answered in the negative.

For fear that some mistake might underlie these experiments, they were repeated scores of times with saponin obtained from different sources, but the same results were always obtained.

CONCLUSIONS.

1. *Saponin dissolves out the coloring matter from the stroma of the red corpuscles of frogs.*
2. *It is a solvent for the whole of both red and colorless corpuscles of birds and mammals.*
3. *It is not a solvent for either the lymph, mucus, or pus corpuscles.*
4. *The white or colorless corpuscle of the blood is not identical with the lymph, mucus or pus corpuscle.*

A question of great clinical and pathological importance here suggests itself, namely, whether the proliferated "white corpuscles" in leucocythæmia can be dissolved by a solution of saponin, as well as the white corpuscles in normal blood. By determining this, we can, perhaps, come to some result which will enable us to diagnose whether in a given case of this disease the increased number of leucocytes is not due to the presence in the blood of numerous lymph or other corpuscles not identical with the white blood corpuscles. My opportunities to pursue the subject in this direction have been few indeed; but I hope the subject will be taken up by physicians who have such cases under observation. In but one case of true leucocythæmia has this method of examination been resorted to; this was in the case of an old man, much emaciated, and in whom the spleen was somewhat enlarged. The white corpuscles in his blood appeared to be increased to at least twenty times the normal number. On adding saponin to a drop of his blood, the white corpuscles disappeared, but a large number of granular corpuscles, some of the size of lymph corpuscles, and others smaller, made

their appearance. These may have been nuclei of the white corpuscles. In several places in the field under the microscope, granular nucleated cells, larger than white corpuscles, were observed.

The blood in a case of pseudo-leucocythæmia was affected by the drug in the same manner as normal blood.

[Saponin immediately arrests the movements of spermatozoa and other ciliated cells. It destroys at once all infusorial life with which it comes in contact, but fails to influence in the least degree the movements of vibrios and bacteria.]

[*To be Continued.*]

ART. IV.—RETROGRADE AND LATERAL MOVEMENTS WITH HYPNOTISM.

BY ISAAC OTT, M. D.

WHEN cold is applied to certain definite regions of the skin in pigeons, they exhibit retrograde movements alternating with fits of stupor. The agent, so far, has been rhigolene, to produce the necessary cold. Ether, when vaporized, was totally unable to produce any effect. The region to which the cold must be applied is the skin of the back of the neck. These phenomena were first observed by Dr. S. Weir Mitchell. I have lately been studying the effect of irritants on the skin of pigeons, and the seat of the phenomena produced. I found that ether, alcohol, chloroform and nitrite of amyl were powerless to produce the effects seen after the application of rhigolene. If, however, bisulphide of carbon was dropped on the skin of the back of the neck, then all the phenomena produced by rhigolene ensued in a marked manner. Thus a single drop of the bisulphide of carbon applied to the back of the neck of the pigeon caused him to retrograde and to pass into states of quietude. When bisulphide of carbon is applied to the skin of the neck in pigeons, the birds run forward as if no agent was acting on them, but suddenly they commence to run backwards, it being quite evidently against their will, as they